AR201-13104A

TEST PLAN FOR METHANOL

CAS 67-56-1

TEST PLAN JUSTIFICATION

SPONSORED BY

THE AMERICAN METHANOL INSTITUTE
TESTING GROUP

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WASHINGTON, DC 2006

METHANOL TEST PLAN

ENDPOINT	INFORMATION AVAILABLE	ACCEPTABLE	TESTING NEEDED
PHYSICAL-CHEMICAL DATA			
Melting Point	YES	YES	NO
Boiling Point	YES	YES	NO
Vapor Pressure	YES	YES	NO
Partition Coefficient	YES	YES	NO
Water Solubility	YES	YES	NO
ENVIRONMENTAL FATE/ PATHWAYS			
Photodegradation	YES	YES	NO
Stability in Water	YES	YES	NO
Transport between Compartments	YES	YES	NO
Biodegradation	YES	YES	NO
ECOTOXICITY			
Acute Toxicity – Fish	YES	YES	NO
Toxicity – Aquatic Invertebrates	YES	YES	NO
Acute Toxicity – Aquatic Plants	YES	YES	NO
TOXICITY			
Acute Toxicity – Mammals	YES	YES	NO
Genetic Toxicity – in vivo	YES	YES	NO
Genetic Toxicity – in vitro	YES	YES	NO
Repeat Dose Toxicity	YES	YES	NO
Toxicity to Reproduction	YES	YES	NO
Developmental Toxicity/Teratogenicity	YES	YES	NO

INTRODUCTION

Methanol occurs naturally in plants and animals. It is a feedstock for chemical syntheses (for formaldehyde, acetic acid, and methyl tertiary-butyl ether) and a solvent in a variety of consumer products,

In humans, methanol is derived both from the diet and from metabolic processes (See robust summary). People ingest low doses of methanol in fruits, vegetables, and fermented beverages as well as indirectly from soft drinks and foods sweetened with aspartame (which breaks down to methanol in the gastrointestinal tract)

There is abundant data on the potential health effects of methanol in humans derived from clinical observations following accidental or intentional ingestion of methanol. Methanol can be highly toxic resulting in nausea, dizziness, metabolic acidosis, and toxicity to the visual system (including blindness), motor disturbances and even death in humans.

PHYSICAL-CHEMICAL DATA

Methanol is a widely used colorless, water-soluble simple alcohol containing one carbon atom. The physical-chemical properties are well known and found in standard references and texts. Original reports on which these citations are based are not available, but the information has been widely accepted based on many years of use. No further testing is need (See robust summary).

ENVIRONMENTAL FATE/PATHWAY

Alcohols generally do not hydrolyze in water. In a soil/water environment, methanol will be present primarily in the water phase. The dissolved methanol will migrate at near the velocity of groundwater except in soils with organic carbon fraction greater than 10 percent. Methanol in aqueous solution exhibited no degradation when exposed to sunlight using an EPA test protocol. Sediment and clay suspension solutions did not photocatalyze the degradation of methanol in aqueous solution during irradiation with UV light. The biodegradation of methanol has been studied under a wide variety of conditions and media, including wastewater, surface water, sediments, groundwater, and in soil microcosms. Methanol is completely degraded and there are no persistent degradation intermediates. No further testing is need (See robust summary).

ECOTOXICITY

A summary of the numerous reports of acute toxicity data shows LC50 values for fish range from 1,400 to 41,000 mg/l. Methanol is sometimes used as a carrier solvent in aquatic toxicology studies. Therefore, numerous chronic toxicity tests have, in fact, been conducted with methanol. For instance, both the USEPA TSCA fish bioconcentration test protocol (40 CFR 797.1560) and the ASTM standard guide for conducting early life-stage toxicity tests with fishes (ASTM E1241-92) specifically allow methanol as a carrier solvent at concentrations not to exceed 0.1 ml/L. Acute toxicity is directly related to the octanol-water partition coefficient; as log Pow increases, toxicity increases (e.g., LC50 decreases). Therefore, neutral compounds with low octanol-water partition coefficients, such as methanol, have very low acute toxicity. In invertebrates acute toxicity data for methanol shows a median effect concentrations (EC50 values) for immobilization range from 10,000 to 38,000 mg/L. Adverse effects (mortality, growth inhibition) occurred when methanol exposures to aquatic plants were in excess of 1,000 mg/L. No further testing is need (See robust summary).

TOXICITY

ACUTE

The acute oral toxicity (LD50) has been reported in rats, mice, monkeys, dogs, swine and rabbits. The 18 studies reported in the robust summary are usually old and details are lacking, but the results are consistent, The LD50 is greater than 5,000 mg/kg in all species tested The acute inhalation toxicity (LC50) has been reported in rats, mice and cats. The 10 studies reported in the robust summary are usually old and details are lacking, but the results are also consistent. The 4 hour LC50 in rats ranged from 64,000 -98,600 ppm. In mice the LC50 was 41,000 ppm and in cats the LC50 was 65,700 ppm. The dermal LD50 in rabbits is 15,840 mg/kg. Based on the large database of old studies and the similar response in various studies, no further testing is need for acute toxicity (See robust summary).

REPEAT DOSE TOXICITY

A majority of the repeat dose studies are inhalation in rats and monkeys. A study in rats and monkeys exposed up to 5,000 ppm, 6 hours/day, 5 days/week for 4 weeks resulted in nasal irritation in rats but not monkeys as the only treatment related effects at the highest dose. NEDO conducted a series of inhalation studies in rats (12 and 24 months), mice (12 and 18 months) and monkeys (2 1 days, 12 months and 30 months). The exposures were 20 plus hours a day, every day. The nearly continuous exposure did not allow much time for clearance, which would be normal in industrial or consumer exposure. The NOAEL in the rat and mouse studies was 100 ppm based on body weight and organ weight effects. No treatment related increase in cancer was observed. In the monkeys various effects were noted at similar doses.

There is also a 90 day gavage study conducted by the EPA in rats. Organ weight and enzyme effects were seen at the highest dose only (2,500 mg/kg). The NOAEL was 500 mg/kg. Methanol was also evaluated in a drinking water study in mice exposed for a lifetime at levels up to 0.899%. No treatment related effects were reported.

Methanol was also evaluated in a skin painting in mice exposed for a lifetime. No treatment related effects were reported. These numerous studies give a good evaluation of repeat exposure effects of methanol, and no further testing is need for repeat dose toxicity (See robust summary).

GENETOXICITY IN VITRO

There are numerous in vitro studies on methanol. They are generally negative and no further testing is need for genetic effects (See robust summary)

GENETOXICITY IN VIVO

There are micronucleus (oral) and cytogenetic assays (inhalation) studies conducted on methanol. They are negative and no further testing is need for genetic effects (See robust summary)

TOXICITY TO REPRODUCTION

Chronic methanol inhalation exposures to 1800 ppm for 2.5 hours per day for up to 1 year did not cause overt maternal toxicity in m. fascicularis females. The menstrual cycles and the ability of females to conceive and give birth to healthy live-born infants were also unaffected. Methanol exposures were associated with a reduction in the length of pregnancy (not dose dependent). No decrease in offspring birth size was observed.

In a two-generation study inhalation exposure had some slight treatment-related effects in rats exposed at 1,000 ppm, but no effects on reproductive performance was noted. Hormone changes were noted in other studies of reproductive effects, but no effects on reproduction were reported. No further testing is need for reproductive toxicity. (See robust summary).

DEVELOPMENTAL TOXICITY/TERATOGENICITY

Pregnant rats exposed by inhalation to 20,000 ppm of methanol for 7 hours per day produced slight maternal toxicity and a significant increase in congenital malformations. A non-statistical increase in

malformation was also reported at 10,000 ppm. inhalation exposure for 20 hours per day caused maternal and fetal toxicity in rats exposed at 5,000 ppm. Methanol is not considered teratogenic in this study. 1,000 ppm was a NOAEL for both the dam and the fetus.

There are several developmental studies in mice, which appears to be more sensitive to methanol than the rats or monkeys. In key inhalation study in mice significant increases in the incidence of exencephaly and cleft palate were observed at 5,000 ppm and above, increased embryo/fetal death at 7,500 ppm and above (including an increasing incidence of full- litter resorptions), and reduced fetal weight at 10,000 ppm and above. A dose-related increase in cervical ribs or ossification sites lateral to the seventh cervical vertebra was significant at 2,000 ppm and above. No signs of maternal toxicity were noted.. The NOAEL for the developmental toxicity in this study was 1,000 ppm. Other special developmental studies in mice looked more closely at nutritional status and at critical stage of gestation to better understand the response in mice.

In a chronic methanol inhalation study in monkeys with daily exposure up to 1800 ppm for 2.5 hours daily for up to 1 year methanol did not cause overt maternal toxicity. The ability of females give birth to healthy live-born infants was also unaffected. Methanol exposures were associated with a reduction in the length of pregnancy (not dose dependent). No decrease in offspring birth size was observed. No further testing is need for developmental toxicity. (See robust summary).

SPECIES DIFFERENCES

The toxicity of methanol varies greatly between different species, toxicity depending on the ability to metabolize formate. In cases of slow metabolism of formate, fatal poisoning occurs as a result of metabolic acidosis and neuronal toxicity, whereas, in animals that readily metabolize formate, CNS depression (coma, respiratory failure, etc.) is usually seen. Sensitive primate species (humans and monkeys) develop increased blood formate concentrations following high level methanol exposure, while resistant rodents, rabbits and dogs do not.

The normal blood concentration of methanol in humans from endogenous sources is less than 0.5 mg/liter (0.02 mmol/litter), but dietary sources may increase blood methanol level. Generally, transient Central Nervous System (CNS) effects appear above blood methanol levels of 200 mg/liter (6 mmol/liter); ocular symptoms appear above 500 mg/liter (16 mmol/liter) and fatalities have occurred in untreated patients with initial methanol levels in the range of 1500-2000 mg/liter (47-62 mmol/liter).

Animal tests were done over the years to obtain predictive information. Investigation of methanol toxicity in animals is somewhat limited because normal rodents exposed to methanol do not display the metabolic acidosis and toxicity to the visual system that occurs in humans.

Incorporation of kinetic parameters and the fraction of inhaled methanol absorbed in humans and rodents into kinetic models predict that an 8-hour exposure to 5,000 ppm methanol will produce some very different results in different species. The blood methanol level in the mouse is 13-l 8 times higher and in the rat it is 5 times higher than humans theoretically exposed to the same 5,000 ppm inhaled level. This species difference may be related to the difference in response of pregnant animals to methanol. The mouse is the most sensitive showing developmental effects below a maternal toxic dose while the rat only response at higher doses that are maternal toxic.

There is abundant data on the potential health effects of methanol in animals and humans. Most information on the human health effects on methanol is derived from clinical observations following accidental or intentional ingestion of methanol. Based on the data in the robust summary no further testing is needed to complete the HPV data needs for methanol.